Scientific Abstract

The use of multiagent chemotherapy combined with surgery and radiation therapy has permitted significant advances in the treatment of many solid tumors, particularly those occurring in childhood. Many sarcomas in both adults and children, however, are relatively resistant to chemotherapy and radiation therapy, leaving surgery as the only treatment option. With current high dose intensity therapies, fewer than half of patients with metastatic neuroblastoma are alive at 5 years from diagnosis, and fewer than 30% of patients with metastatic sarcomas are alive at 5 years. Therefore, new treatment options are desperately needed for these diseases.

Attenuated Herpes simplex virus (HSV) mutants engineered with deletions of normally critical genetic functions dispensable in cancer cells are being actively pursued as novel therapeutic agents. HSV1716 is derived from the HSV-1 strain 17^{+}, but is deleted for the gene encoding ICP34.5, reducing its virulence and causing it to be permissive for replication selectively in rapidly dividing cells. It has been used in several previous clinical trials and has shown safety in adults. Therefore, we propose a phase I clinical trial to test the safety of direct intratumoral injections of HSV1716 in patients with high-risk sarcomas and neuroblastomas in adolescents and young adults.

Patients will be eligible if they have relapsed or refractory disease. Metastatic patients at relapse will be included, in which case a single lesion will be chosen for administration. Two dose strata will be planned, based on doses already shown to be safe in adults. The virus will be administered directly into the tumor via Ultrasound or CT-guided injection by interventional radiology. Because the virus will be administered locally and not systemically, the dose will not be adjusted for patient size. Patients will be able to receive a total of four injections at least 3 weeks apart to determine the safety of single as well as multiple administrations.

As part of the trial, we will include biology studies including pre- and post-therapy measurements of anti-HSV1 immunity and polymerase chain reaction detection of viremia. In cases where a post-therapy tumor biopsy is clinically indicated, the extent of viral replication by in situ hybridization or PCR and correlation with tumor cell necrosis will be evaluated.

This study will determine whether doses shown to be safe in adults are also safe for adolescents and young adults. The results from this trial will facilitate the design and implementation of subsequent clinical trials of HSV1716 for sarcomas and neuroblastomas.